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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

04292681.6

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

1-N-phenylamino-1H-imidazole derivatives and pharmaceutical compositions containing them

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The present invention relates to 1-N-phenylamino-1H-imidazole derivatives and to pharmaceutical compositions containing them.

The invention generally relates to the field of hormone- and non hormone-dependent cancer and endocrine disorders.

Aromatase is the physiological enzyme responsible for the specific conversion of androgens such as androstenedione or testosterone, into estrogens such as estrone and estradiol, respectively (Simpson ER et al., Endocrine Reviews, 1994, 15 : 342-355). Inhibition of aromatase is, therefore, a strategy of choice to interfere with normal or pathological estrogen-induced or estrogen-dependent biological processes such as female sexual differentiation, ovulation, implantation, pregnancy, breast and endometrial cell proliferation as well as regulations of spermatogenesis or prostate cell proliferation in male or of non-reproductive functions such as bone formation or immune T cell and cytokine balance (see Simpson ER et al., Recent Progress in Hormone Research, 1997, 52 : 185-213 and the whole issues of Endocrine Related Cancer (1999, volume 6, n°2) and Breast Cancer Research Treatment (1998, volume 49, supplement n°1)).

The enzyme steroid sulfatase (E.C. 3.1.6.2., STS) catalyses the hydrolysis of estrone sulfate to estrone and the DHEA sulfate to DHEA (Dibbelt L, Biol. Chem, Hoppe-Seyler, 1991, 372, 173-185 and Stein C, J. Biol. Chem., 1989, 264, 13865-13872).

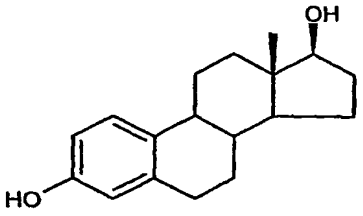
The steroid sulfatase pathway has been the focus of recent interest in the context of breast cancer, with regard to the local intra-tissue formation of estrogens from the abundant circulating pool of estrone sulfate (E_1S) (Pasqualini JR, J. Steroid Biochem. Mol. Biol., 1999, 69, 287-292 and Purohit A, Mol. Cell. Endocrinol., 2001, 171, 129-135).

Inhibition of this enzyme would prevent E_1S from yielding free estrone (E_1), which can be transformed into estradiol (E_2) by enzymatic reduction. In addition to the estrone sulfatase pathway, it is now believed that another potent estrogen, androstenediol (adiol) obtained from DHEA after hydrolysis of DHEA-S, could be another important contributor, in the support of growth and development of hormone-dependent breast tumors.

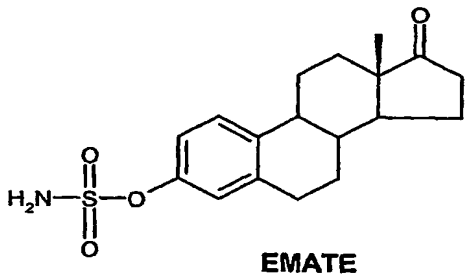
The formation of estrogens in women is schematically represented in figure 1.

In patients with hormone-dependent cancers, aromatase inhibitors are currently used to prevent estrogen synthesis. However, clinical trials showed a relative lack of efficacy for patients with estrogen receptor-positive tumors (Castiglione-Gertsch M, Eur. J. Cancer, 1996, 32A, 393-395 and Jonat W, Eur. J. Cancer, 1996, 32A, 404-412). As an explanation, steroid sulfatase pathway could be another important route for estrogen formation in breast tumors.

EMATE (Ahmed S, Curr. Med. Chem., 2002, 9, 2, 263-273), estrone-3-sulfamate, is the historical standard steroidal sulfatase inhibitor but has the major drawback of being estrogenic because of its mechanism of inhibition: the sulfamate moiety is cleaved during the process of enzyme inactivation, which releases E_1, not from E_1S but from EMATE itself (Ahmed S, J. Steroid Biochem. Mol. Biol., 2002, 80, 429-440).

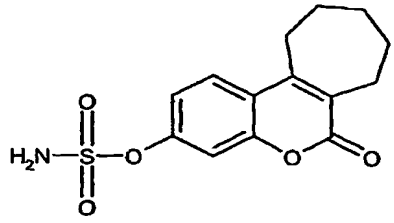


Estradiol



EMATE

Other non-steroid sulfamate compounds which release derivatives without estrogenic properties have been presented as acceptable drug candidates such as 6,6,7-COUMATE, a standard non-estrogenic sulfatase inhibitor from the literature (Purohit A, Cancer Res, 2000, 60, 3394-3396).



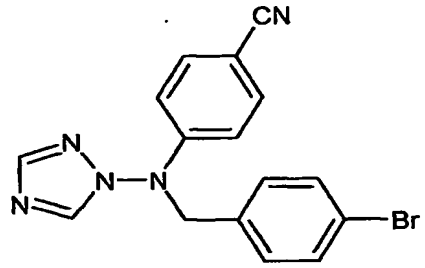
6,6,7 COUMATE

Human carbonic anhydrases catalyse the conversion between carbon dioxide (CO_2) and the bicarbonate ion (HCO_3^-), and are involved in physiological and

pathological processes. They include hormone-dependent and non-hormone-dependent cancerogenesis, metastasis invasive process and hypoxic tumors that express these enzymes which are less responsive to classical chemo/radio-therapy inhibitors. In particular, EMATE was found to have a human carbonic anhydrase inhibitory potency similar to that of acetazolamide, a well-known sulfonamide human carbonic anhydrase inhibitor (Winum J and al., J. Med. Chem. 2003, 46, 2197-2204).

It is therefore of particular interest to have compounds with at least one, preferably at least two of the following activities: aromatase inhibition, steroid sulfatase inhibition and carbonic anhydrase inhibition.

Recently, B. Potter et al. (J. Med. Chem., 46, 2003, 3193-3196) reported that sulfamoylated-derivatives of the aromatase inhibitor YM 511 inhibited sulfatase and aromatase activity in JEG-3 cells.



YM 511

Compounds presented as useful for the treatment of estrogen-dependent diseases, are described in US 2003/0008862A. Imidazole derivatives with anti-aromatase properties are described in WO 2004/054983.

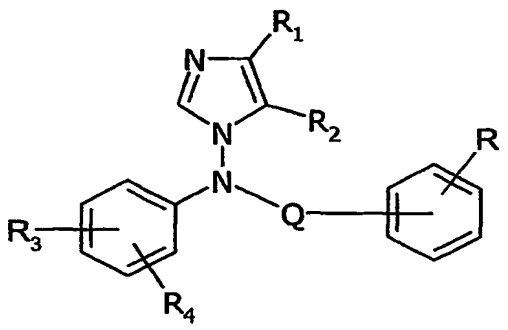
It has now been found that imidazole derivatives which contain a 1-N-phenylamino group, demonstrate an unexpectedly high potency to inhibit aromatase and/or steroid sulfatase and/or carbonic anhydrase.

Accordingly, one object of this invention is to provide 1-N-phenylamino-1H-imidazole derivatives, which are potent aromatase and/or steroid sulfatase and/or carbonic anhydrase inhibitors.

Another object of this invention is to provide a pharmaceutical composition containing, as active ingredient, a 1-N-arylamino-1H-imidazole derivative as depicted below.

A further object of this invention is to provide the use of 1-N-phenylamino-1H-imidazole derivatives in the manufacture of a medicament for treating or preventing various diseases and for managing reproductive functions in women, in men as well as in female and male wild or domestic animals.

The 1-N-phenylamino-1H-imidazole derivatives of this invention are represented by the following general formula (I):



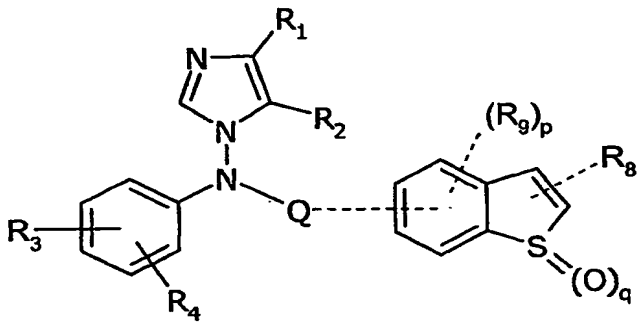
(I)

and acid addition salts and stereoisomeric forms thereof, wherein:

- R_1 and R_2 are each independently hydrogen, a $(C_1\text{-}C_6)$alkyl or a $(C_3\text{-}C_8)$cycloalkyl ; or R_1 and R_2 together form a saturated or unsaturated 5-, 6- or 7- membered carbocyclic ring;
- Q is $(CH_2)_m\text{-}X\text{-}(CH_2)_n\text{-}A\text{-}$;
- A is a direct bond or O, S, SO, SO_2, NR_5;
- X is a direct bond, CF_2, O, S, SO, SO_2, C(O), NR_5 or CR_6R_7;
- m and n are each independently 0, 1, 2, 3 or 4;
- R_3 and R_4 are each independently a $-(CY_1Y_2)_r\text{-}Z$ group;
- Z is hydrogen or a hydroxy, cyano, halogen, nitro, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, benzyloxy, trifluoromethyl, $(C_1\text{-}C_6)$alkylthio, $(C_1\text{-}C_6)$alkylsulfonyl, acyl, $(C_1\text{-}C_6)$alkoxycarbonyl, $-NR_{10}R_{11}$, $-OPO(OR_{10})_2$, -OCHO, $-COOR_{10}$, $-SO_2NR_{10}R_{11}$, $-OSO_2NR_{10}R_{11}$, $-SO_2OR_{10}$, $-OSO_2OR_{10}$, $-SSO_2NR_{10}R_{11}$, $-CONR_{10}R_{11}$, $-OCONR_{10}R_{11}$, $-OCSNR_{10}R_{11}$, $-SCONR_{10}R_{11}$, $-SCSNR_{10}R_{11}$, $-NR_{12}SO_2NR_{10}R_{11}$, tetrazolyl group, $-NR_{10}CONR_{11}OH$, $-NR_{10}SO_2NR_{11}OH$, -NOH-CHO, $-NOHSO_2NR_{10}R_{11}$, or $-OSO_2NR_{10}OH$;
- Y_1 and Y_2 are each independently H or F;
- r is 0, 1 or 2;

- R_5, R_6, R_7, R_{10}, R_{11} and R_{12} are each independently hydrogen, a $(C_1$-$C_6)$alkyl or a $(C_3$-$C_8)$cycloalkyl; R_{10} can also be a salt; R_{10} and R_{11} can also form, together with the nitrogen atom to which they are bound, a 5- to 7-membered heterocycle containing one or two heteroatoms selected from O, S and N;
- the aromatic ring together with the R group represent a moiety that inhibits the sulfatase enzyme.

A preferred embodiment of the above compounds is represented by general formula (II):



(II)

wherein:

- R_1, R_2, R_3, R_4 and Q are as defined for the compounds (I);
- R_8 and R_9 are each independently a $-(CY_1Y_2)_r$-Z group;
- Y_1, Y_2 and Z are as defined for the compounds (I);
- p is 1, 2, 3 or 4; when p is 2, 3 or 4 the radicals R_9 can be the same or different;
- q is 0,1 or 2.
- The dotted line means that Q and/or R_8 and/or R_9 can be on any position of the benzothiophene ring.

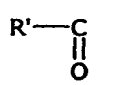
The present invention also concerns the addition salts of the invention compounds or the stereoisomeric forms thereof, when they exist.

In the description and claims, the term "$(C_1$-$C_6)$alkyl" is understood as meaning a linear or branched hydrocarbon chain having 1 to 6 carbon atoms. A $(C_1$-$C_6)$alkyl radical is for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl or hexyl radical. Preferred alkyl radicals are those having 1, 2 or 3 carbon atoms.

The term "halogen" is understood as meaning a chlorine, bromine, iodine or fluorine atom.

The term "(C_3-C_8)cycloalkyl" is understood as meaning a saturated monocyclic hydrocarbon having 3 to 8 carbon atoms. A (C_3-C_8)cycloalkyl radical is for example a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl radical.

The term "(C_1-C_6)alkoxy" is understood as meaning a group OR in which R is a (C_1-C_6)alkyl as defined above. A (C_1-C_6)alkoxy radical is for example a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, n-pentyloxy or isopentyloxy radical. Preferred alkoxy radicals are those having 1, 2 or 3 carbon atoms.

The term "acyl" is understood as meaning a group  in which R' is hydrogen or a (C_1-C_4)alkyl wherein the term "alkyl" is as defined above. An acyl radical is for example a formyl, an acetyl, a propionyl, a butyryl or a valeryl radical. Preferred acyl radicals are formyl and acetyl.

In the definition of R_{10}, a "salt" is understood as meaning an alkali metal salt or alkaline earth metal salt, such as a sodium, potassium, magnesium or calcium salt, or a salt with an ammonium or with an organic amine such as triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. In the context of the invention, this applies to groups having an OR_{10} moiety.

The 5- to 7-membered heterocycle can be saturated or unsaturated, and includes for example tetrazole, triazole, pyrazole, pyrazolidine, imidazolidine, piperidine, piperazine, morpholine, pyrrolidine.

Compounds of formula (I) form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like or with organic carboxylic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid and the like. Especially preferred are those salts which are pharmaceutically acceptable.

Among the compounds of formula (I) and (II), those which fulfil at least one of the following conditions are preferred:

- R_1 and R_2 are each independently hydrogen or $(C_1$-$C_6)$alkyl;
- R_3 is hydrogen, halogen or cyano;
- R_4 is hydrogen, halogen, cyano, $(C_1$-$C_6)$alkoxy, $-NR_{10}R_{11}$, $-OSO_2NR_{10}R_{11}$ or $-NR_{12}SO_2NR_{10}R_{11}$;
- R_{10}, R_{11} and R_{12} are each independently hydrogen or $(C_1$-$C_6)$alkyl.

Among the compounds of formula (II), those which fulfil at least one of the following conditions are preferred:

- R_8 is $-OSO_2NR_{10}R_{11}$, $-NR_{12}SO_2NR_{10}R_{11}$;
- R_9 is hydrogen, halogen, nitro, $COOR_{10}$, or cyano;
- q is 0, 1, 2.

Especially preferred compounds of formulae (I) and (II) are those where:

- m is 0 or 1;
- r is 0, 1 or 2;
- R_1, R_2 and R_4 are each hydrogen;
- R_3 is cyano;
- Y_1 and Y_2 are both H or F.

Most preferred compounds are compounds of formulae (I) and (II) in which:

- Q is $-(CH_2)_m$-X- where m is 0, 1 or 2;
- X is a direct bond, SO_2 or CO.

By virtue of their capability to inhibit the enzymes aromatase and/or steroid sulfatase and/or carbonic anhydrase, the compounds of the present invention can be used alone or in combination with other active ingredients for the treatment or the prevention of any hormone or non hormone-dependent cancer, in humans as well as in wild or domestic animals. Because of their inhibition activity of aromatase and/or steroid sulfatase, the compounds of the invention are suitable for the management of estrogen-regulated reproductive functions, in humans as well as in wild or domestic animals.

In the treatment or prevention of the above conditions, the compounds of the invention can be used alone or in combination with an antiestrogen, a SERM (selective estrogen receptor modulator), an aromatase inhibitor, a carbonic anhydrase inhibitor, an antiandrogen, a steroid sulfatase inhibitor, a lyase inhibitor, a progestin, or a LH-RH agonist or antagonist. The compounds of the invention can also be used in combination with a radiotherapeutic agent; a

chemiotherapeutic agent such as a nitrogenated mustard analogue like cyclophosphamide, melphalan, iphosphamide, or trophosphamide; an ethylenimine like thiotepa; a nitrosourea like carmustine; a lysed agent like temozolomide or dacarbazine; an antimetabolite of folic acid like methotrexate or raltitrexed; a purine analogue like thioguanine, cladribine or fludarabine; a pyrimidine analogue like fluorouracil, tegafur or gemcitabine; an alkaloid of vinca or analogue like vinblastine, vincristine or vinorelbine; a podophyllotoxin derivative like etoposide, taxanes, docetaxel or paclitaxel; an anthracycline or analogue like doxorubicin, epirubicin, idarubicin or mitoxantrone; a cytotoxic antibiotic like bleomycin or mitomycin; a platinum compound like cisplatin, carboplatin or oxaliplatin; a monoclonal antibody like rituximab; an antineoplastic agent like pentostatin, miltefosine, estramustine, topotecan, irinotecan or bicalutamide; or with a prostaglandin inhibitor (COX 2/COX 1 inhibitor).

The compounds of the invention can also be used for the control or management of estrogen-regulated reproductive functions such as male or female fertility, pregnancy, abortion or delivery, in humans as well as in wild or domestic animal species, alone or in combination with one or several other therapeutic agents such as a LH-RH agonist or antagonist, an estroprogestative contraceptive, a progestin, an antiprogestin or a prostaglandin inhibitor.

Breast tissue being a sensitive target of estrogen-stimulated proliferation and/or differentiation, inhibitors of aromatase and/or steroid sulfatase and/or carbonic anhydrase can be used in the treatment or prevention of benign breast diseases in women, gynecomastia in men and in benign or malignant breast tumors with or without metastasis both in men and women or in male or female domestic animals. The compounds of the invention can also be used in the treatment or prevention of benign or malignant disease of the uterus or the ovary. In each case, the compounds of the invention can be used alone or in combination with one or several other sexual endocrine therapeutic agents such as an antiandrogen, an anti-estrogen, a progestin or a LH-RH agonist or antagonist.

As the enzyme steroid sulfatase transforms DHEA sulfate into DHEA, a precursor of active androgens (testosterone and dihydrotestosterone), the compounds of the invention can be used in the treatment or prevention of androgen-dependent diseases such as androgenic alopecia (male pattern loss) (Hoffman R et al., J.

Invest. Dermatol., 2001, 117, 1342-1348), hirsutism, acne (Billich A et al., WO 9952890), benign or malignant diseases of the prostate or the testis (Reed MJ, Rev. Endocr. Relat. Cancer, 1993, 45, 51-62), alone or in combination with one or several other sexual endocrine therapeutic agents such as an antiandrogen, an antiestrogen, a SERM, an antiaromatase, a progestin, a lyase inhibitor or a LH-RH agonist or antagonist.

Inhibitors of steroid sulfatase are also potentially involved in the treatment of cognitive dysfunction, because they are able to enhance learning and spatial memory in the rat (Johnson DA, Brain Res, 2000, 865, 286-290). DHEA sulfate as a neurosteroid affects a number of neurotransmitter systems including those involving acetylcholine, glutamate, and GABA, resulting in increased neuronal excitability (Wolf OT, Brain Res. Rev, 1999, 30, 264-288). The compounds of the present invention are thus also useful for enhancing the cognitive function, especially for the treatment of senile dementia, including Alzheimer's diseases, by increasing the DHEA levels in the central nervous system.

In addition, estrogens are involved in the regulation of the balance between Th_1 and Th_2 predominant immune functions and may therefore be useful in the treatment or prevention of gender-dependent auto-immune diseases such as lupus, multiple sclerosis, rheumatoid arthritis and the like (Daynes RA, J. Exp. Med, 1990, 171, 979-996). Steroid sulfatase inhibition was further shown to be protective in models of contact allergy and collagen-induced arthritis in rodents (Suitters AJ, Immunology, 1997, 91, 314-321).

Studies using 2-MeOEMATE have shown that steroid sulfatase inhibitors have potent estradiol-independent growth-inhibitory effect (MacCarthy-Moorogh L, Cancer Research, 2000, 60, 5441-5450). A decrease in tumor volume was surprisingly observed with the compounds of the invention, with low tumor steroid sulfatase inhibition. In view of this, the compounds of the invention could lead to a decrease in cellular division because of the large interaction between such new chemical entities and the microtubular network within the cancerous cell, whatever the tissue, including breast, endometrium, uterus, prostate, testis or metastasis generated therefrom. The compounds of the invention could therefore be useful in the treatment of non-estrogen dependent cancer.

The compounds of the invention are of particular value for the treatment or prevention of estrogen-dependent diseases or disorders, i.e. estrogen-induced or estrogen-stimulated diseases or disorders (Golob T, Bioorg. Med. Chem., 2002, 10, 3941-3953).

In addition, the compounds of the present invention are inhibitors of carbonic anhydrase (CA). This property could explain the interest of such compounds in non-hormone-dependent cancer. Immunohistochemical studies of CA II have shown that it is expressed in malignant brain tumors (Parkkila A-K. et al., Histochem. J., 1995, 27: 974-982) and gastric and pancreatic carcinomas (Parkkila S et al., Histochem. J., 1995, 27: 133-138), and recent evidence has shown that CA IX and XII are also expressed in some tumors and may be functionally related to oncogenesis. Ivanov et al. (Proc. Natl. Acad. Sci. USA, 1998, 95: 12596-12601) recently hypothesized that tumor-associated CA IX and XII may be implicated in acidification of the extracellular medium surrounding cancer cells, which would create a microenvironment conducive to tumor growth and spreading. It has been shown that acetazolamide markedly inhibited invasion capacity in four renal cancer cell lines (Parkkila S et al., Proc. Natl. Acad. Sci. USA, 2000, 97: 2220-2224), an effect attributable to CA II, IX, and XII, which were expressed in these cells. Leukemia cells can easily spread from bone marrow to other organs via circulation, but various leukemias differ in their ability to form extramedullary tumors i.e., metastases. If CA activities were essential for invasion by other cancer cells, one could analogously predict that active CA(s) could also function in leukemia cells.

As used herein, the term "combined" or "combination" refers to any protocol for the co-administration of a compound of the invention and one or more other pharmaceutical substances, irrespective of the nature of the time of administration and the variation of dose over time of any of the substances. The co-administration can for example be parallel, sequential or over a period of time.

For the treatment/prevention of any of the above-mentioned diseases or disorders, the compounds of the invention may be administered, for example, orally, topically, parenterally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. These

dosage forms are given as examples, but other dosage forms may be developed by those skilled in the art of formulation, for the administration of the compounds of the invention. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of humans, the compounds of the invention are effective in the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc.

The pharmaceutical compositions containing the active ingredient(s) may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient(s) in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient(s) is (are) mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules

wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active ingredient(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil, for example peanut oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or acetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient(s) in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present. The pharmaceutical compositions of the invention may also be in the form of an oil-

in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or peanut oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soybean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Dosage levels of the order of from about 0.0001 mg to about 20 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.1 mg to about 2000 mg per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 0.1 mg to about 400 mg of compound of the invention, typically 0.1 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 100 mg, 200 mg or 400 mg.

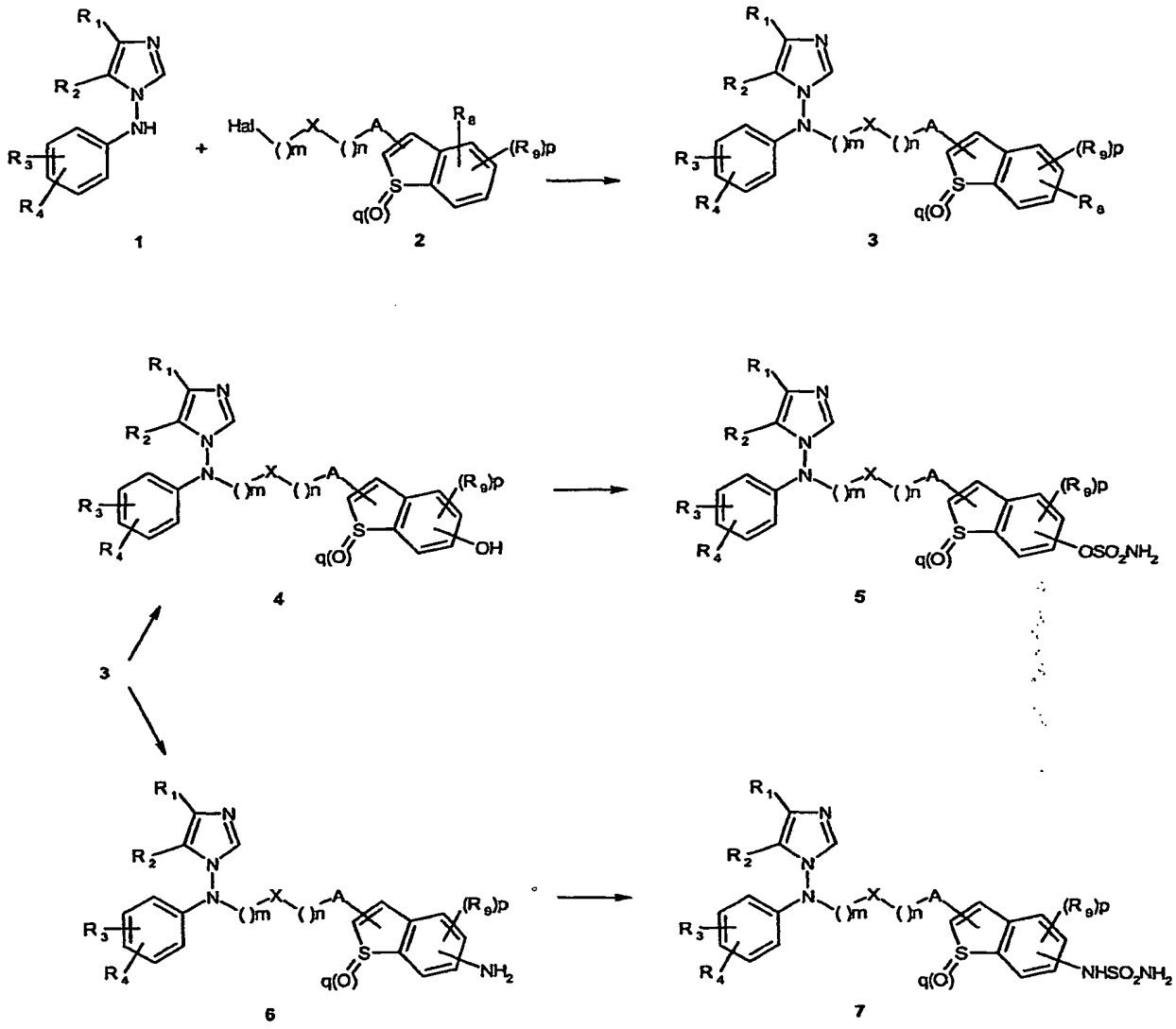
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of

excretion, drug combination and the severity of the particular disease undergoing therapy.

According to another object, the invention relates to a method for the treatment or prevention of the above-mentioned diseases, disorders or conditions. The method comprises administering to a subject (human or animal) in need thereof a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable acid addition salt thereof.

The compounds of the invention can be prepared following the general schemes Ia and Ib, in which $()_m$ represents $(CH_2)_m$ and $()_n$ represents $(CH_2)_n$.

Scheme I a



According to scheme I a, compounds (3) can be obtained by condensation of the N-imidazoloaniline (1) with halogeno derivatives, alcoyl derivatives, sulfonyl derivatives or sulfinyl derivatives (2) using standard conditions (March J., *Advanced Organic Chemistry*, Fourth edition, Wiley Interscience, New-York). Most of the halogeno derivatives, alcoyl derivatives, sulfonyl derivatives or

sulfinyl derivatives (2) are commercially available or are synthesized by usual chemistry methods (see experimental part).

If R_8 is ester, saponification of compound (3) gives carboxylic derivative by usual chemistry methods.

If R_8 is sulfamide, it can be directly obtained with correct substituted alcoyl derivative or halogeno derivative (2).

if R_8 is cyano group, reaction with sodium azide gives tetrazolyl group (Kiyoto K., *Synthesis*, 1998, 910-14).

Deprotection of methoxy or benzyloxy benzothiophene (3) with tribromoborane (McOmie. J.F.W, *Tetrahedron*, 1968, 24, 2289-92) or by hydrogenation (Felix A., *J Org Chem*, 1978, 43, 4194-97) gives the hydroxy benzothiophene (4). Reduction of nitro benzothiophene compound (3) by stannous chloride gives amino-benzothiophene (6) (Matassa V., *J Med Chem*, 1990, 33, 2621-29).

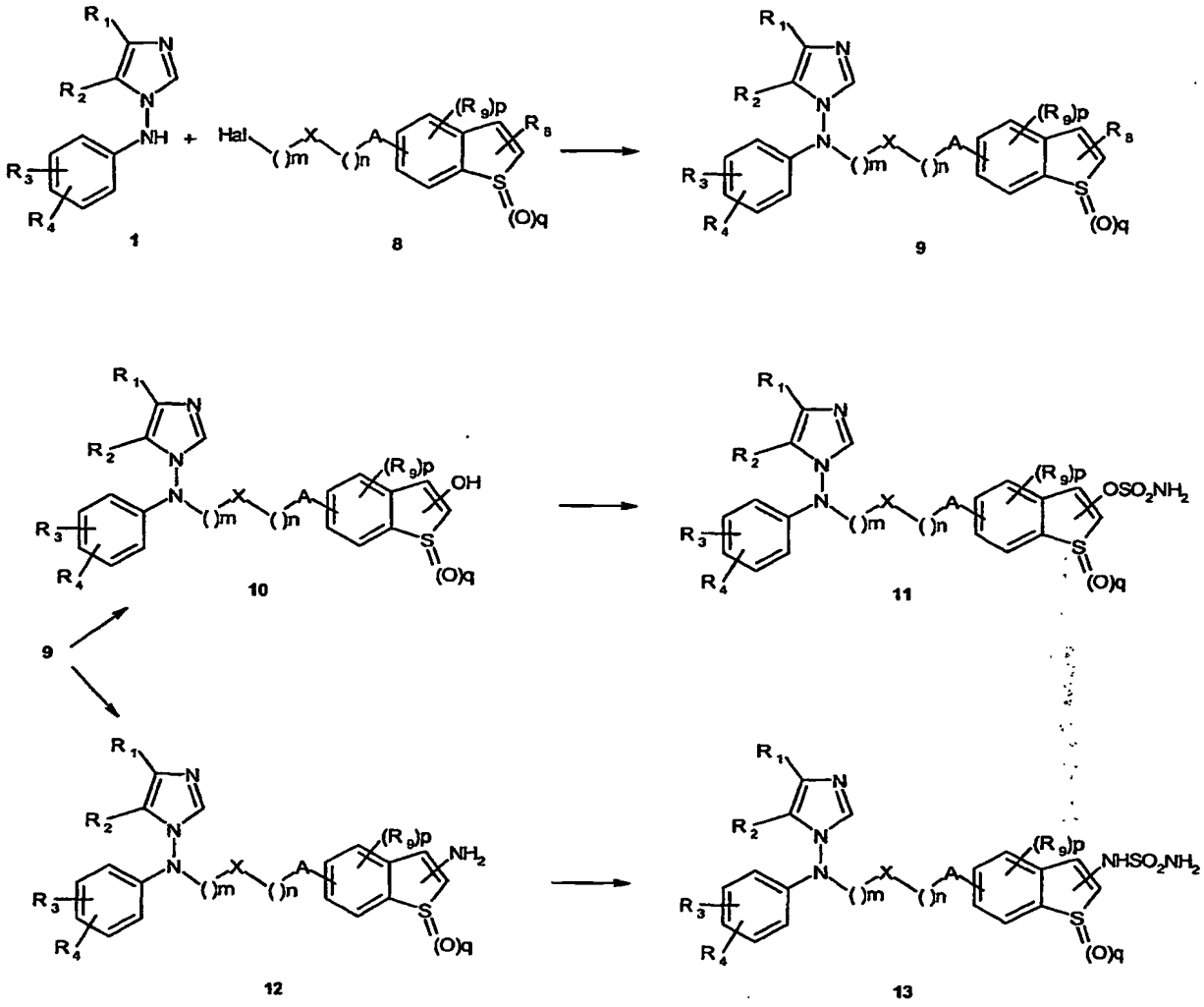
These compounds are transformed into the corresponding sulfamates (5) or aminosulfonylamines (7) by treatment with sodium hydride and sulfamoyl chloride (Nussbaumer. P, *J Med Chem*, 2002, 45, 4310-20), or by reaction with sulfamoyl chloride in dimethylacetamide (DMAc) (Makoto O, *Tetrahedron letters*, 2000, 41, 7047-51).

Oxidation of sulphur on benzothiophene by hydrogen peroxide in trifluoroacetic acid, following the conditions described by GRIVAS S. and RONNE E. (*Acta Chemica Scandinavia*, 1995, 49, 225-229) or by meta-chloro-per-benzoic acid in methylene chloride gives the oxydised benzothiophenes.

Reduction of amide, ketone or oxidised sulphur function is performed following the conditions described by Ellefson C. (*J Med Chem*, 1981, 24, 1107-10), Hajos J. (*Complex Hydrides*, Elsevier, New York, 1979) or Drabowicz S. (*Org Prep Proced Int*, 1977, 9, 63-83) and Bordwell J. (*J Am Chem Soc*, 1951, 73, 2251-53).

These oxidation and reduction steps can be effective at any steps of synthesis process.

Scheme I b



According to scheme I b, compounds (9) are synthesized following the same synthetic methods as for compounds (3) starting from compounds (1) and (8). 3-Halogeno benzothiophene derivative (9) treated by aqueous metal hydroxide (Svoboda J., *Collect Czech Chem comm*, 2000, 65, 7, 1082-92 or Sall D., *J Med Chem*, 2000, 43, 4, 649-63) gives 3-hydroxy benzothiophene derivative (10) or treated by aqueous ammonia in acetone or ethanol (Bordwell F., *J. A. C. S.*, 1948, 70, 1955-58) gives 3-amino benzothiophene derivative (12).

2-Hydroxy benzothiophene derivative (10) or 2-amino benzothiophene derivative (12) are performed respectively by deprotection of 2-methoxy benzothiophene derivative (9) with pyridine hydrochloride (Cannizzo S., *J Heterocyclic Chem*, 1990, 27, 2175-79) and by reduction of 2-nitro benzothiophene compound (9) by stannous chloride (Matassa V, *J Med Chem*, 1990, 33, 2621-29).
These compounds (10) and (12) can be sulfamoylated to give (11) and (13) using the same conditions as for the synthesis of compounds (5) or (7).

Deprotonation of 2-H-benzothiophene derivative (9) with lithium amides or alkyls leads to lithiation at C-2 position. Addition of sulfuryl chloride yielded chlorosulfonyl compound that is treated by aqueous ammonia in acetone (Graham S., *J Med Chem*, 1989, 32, 2548-54) to give 2-sulfonamide benzothiophene derivative (9) or addition of dry ice followed by hydrolysis gives 2-carboxylic acid benzothiophene derivative (9) (Matecka D., *J Med Chem*, 1997, 40, 705-16).

3-Carboxylic or carboxamide benzothiophene derivative (9) is prepared by treatment of 3-H-benzothiophene derivative with trichloroacetyl chloride/aluminium chloride followed by hydrolysis with water (Bonjouklian R., *Synth Comm*, 1985, 15, 8, 711-13) or aqueous ammonia (Turnbull K., *J Heterocycl Chem*, 2000, 37, 2, 383-88).
3-Sulfonamide derivative is prepared following the conditions described by Chapman N. *(J. Chem. Soc.*, 1970, 18, 2431-35) or Hageman W. (Ger. Offen., 3435173,11 April 1985).
Oxidation of sulfur on benzothiophene and reduction of carboxamide, ketone, oxydised sulphur function can be performed at any step of synthesis following the same conditions already presented in this description.

The groups described for R_3, R_4, R_8 and R_9 can be obtained by usual chemistry methods (for references see review on sulfatase (Nussbaumer P, *Medecinal Research*, 2004, 24, 4, 529-76), on carbonic anhydrase (Supuran C T, *Carbonic anhydrase*, 2004, C R C press) and articles from Park J D (*J Heterocycl Chem*,

2000, 37, 2, 383-88), Schreiner E P (*Bioorg Med Chem Lett*, 2004, 14, 4999-5002) and Taylor S D (*Bioorg Med Chem Lett*, 2004, 14, 151-155).

The following examples are intended to illustrate and not to limit the scope of the invention.

PREPARATION OF BENZOTHIOPHENE DERIVATIVES (2) AND (8)

EXAMPLE 1

1-Chloro-3-(3-methoxyphenyl)sulfanyl-propan-2-one

To a stirred solution of 1,3-dichloro-2-propanone (12.70 g, 0.1 mol) in methanol/water (100 ml, 1:3) at 0°C is added a suspension of 3-methoxybenzenethiol (14.02 g, 0.1 mol) and sodium hydroxide (4.00 g, 0.10 g) in water (100 ml). The mixture is stirred at 0°C for 7 h and at room temperature for 10 h. The precipitated product is extracted with dichloromethane (100 ml), washed with water (80 ml), and dried with sodium sulphate. After removal of the solvent, we obtained the good product (oil, 18.70 g).

^{1}H-NMR ($CDCl_3$): 3.80 (s, 3H), 3.83 (s, 2H), 4.29 (s, 2H), 6.78 (dd, 1H), 6.98 (d, 1H), 6.90 (dd, 1H), 7.21 (t, 1H).

EXEMPLE 2

3-Chloromethyl-6-methoxy-benzothiophene

A solution of the above thio compound (17.50 g, 75.85 mmol) in CH_2Cl_2 (1700 ml) was added dropwise to a solution of $BF_3.Et_2O$ (10.60 ml, 83.44 mmol) in CH_2Cl_2 (100 ml) at room temperature under nitrogen atmosphere. The mixture was stirred overnight and after hydrolysis with aqueous $NaHCO_3$ solution, the reaction mixture was stirred until both phases became clear. The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum to give an oil (18.00 g). Flash chromatography on silica gel (toluene /petroleum spirit 40-60°C : 5/5) yielded a 1:10 mixture of 3-chloromethyl-4-methoxy-

benzothiophene: 3-chloromethyl-6-methoxy-benzothiophene as an oil (12.35 g, 58 %).

Major isomer ^{1}H-NMR ($CDCl_3$): 3.89 (s, 3H), 4.82 (s, 2H), 7.08 (dd, 1H), 7.30 (s, 1H), 7.35 (d, 1H), 7.78 (d, 1 H).

EXEMPLE 3

3-Bromo-6-benzyloxy-benzothiophene

N-bromosuccinimide (15.70 g, 83.92 mmol) and p-toluenesulfonic acid (2.70 g, 15.68 mmol) were added to a solution of 6-benzyloxy-benzothiophene (Zhengying C., CN 1370533 A, 21.2 g, 88.33 mmol) in 1,2-dichloroethane (120 ml). The mixture was maintained at 80°C for 35 min, cooled in an ice bath, and the succinimide was removed by filtration. The solution was extracted with saturated sodium bicarbonate solution, dried over Na_2SO_4, filtered, and concentrated under vacuum to give an oil. Crystallisation from pentane afforded a white solid (21.60 g, 92 %, mp: 68°C).

^{1}H-NMR ($DMSOd_6$): 5.14 (s, 2H), 7.08 (dd, 1H), 7.25-7.55 (m, 6H), 7.65 (d, 1H), 7.76 (d, 1H).

EXEMPLE 4

3-Bromo-6-benzyloxy-benzothiophene-1,1-dioxyde

To a solution of 3-bromo-6-benzyloxy-benzothiophene (2.00 g, 6.27 mmol) in dichloromethane (50 ml) and trifluoroacetic acid (1.5 ml) was added 35% aqueous hydrogen peroxide (2.00 ml, 19.54 mmol). After 8 h at 50°C the mixture was hydrolysed with saturated aqueous $NaHCO_3$, extracted with dichloromethane, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude product. Flash chromatography on silica gel (toluene / ethyl acetate: 9/1) yielded a limpid oil (1.10 g, 55%).

^{1}H-NMR ($DMSOd_6$): 5.20 (s, 2H), 7.20-7.60 (m, 7H), 7.72 (d, 1H), 7.83 (s, 1H).

EXEMPLE 5

(6-Benzyloxy-benzothien-2-yl)methanol

To a solution of 6-benzyloxy-benzothiophene-2-carbaldehyde (described by Nomura Y., WO 9635688 A1, 6.50 g, 24.20 mmol) in THF (50 ml) was added dropwise to a –30°C cooled suspension of $LiAlH_4$ (0.85 g, 22.26 mmol). After warming up to room temperature the mixture was stirred overnight , cooled to –10°C, hydrolyzed with ice water, extracted with dichloromethane, dried over Na_2SO_4, filtered and concentrated under vacuum to give the crude product. Flash chromatography on silica gel (toluene / ethyl acetate: 7/3) yielded a limpid oil (4.50 g, 69%).

^{1}H-NMR ($DMSOd_6$): 4.68 (s, 2H), 5.13 (s, 2H), 5.60 (s, 1H), 7.00 (dd, 1H), 7.14 (s, 1H), 7.25-7.80 (m, 7H).

EXEMPLE 6

6-Benzyloxy-2-(chloromethyl)-benzothiophene

Sulfonyl chloride (20 ml) is added to a solution of (6-benzyloxy-benzothien-2-yl) methanol (4.20 g, 15.50 mmol) in dichloromethane (40 ml). The mixture was maintained at reflux for 2 h, cooled at room temperature then concentrated under vacuum to give 4.20 g as an oil.

^{1}H-NMR ($CDCl_3$): 4.75 (s, 2H), 5.04 (s, 2H), 6.95 (dd, 1H), 7.10 (s, 1H), 7.20-7.60 (m, 7H).

PREPARATION OF BENZOTHIOPHEN-IMIDAZOL DERIVATIVES (3), (4), (6), (9), (10) AND (12)

EXEMPLE 7

5-Nitro-[N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)]-benzothiophene-2-carboxamide

5-Nitro-benzothiophene-2-carbonyl chloride (commercial compound, 10.00 g, 41.00 mmol) was added to a mixture of 4-[N-(1H-imidazol-1-yl)amino]benzonitrile (7.55 g, 41.00 mmol), TEA (20 ml, 143.00 mmol) in dry THF (150 ml) at room temperature. The mixture was then stirred at room temperature overnight and the precipitate was filtrated, washed with THF, water

to give the crude product as a solid (9.26g). Crystallization with ethanol yielded white crystals (3.50 g, mp: 221°C).

^{1}H-NMR (DMSO d_6): 7.10 (s, 1H), 7.54 (s, 1H), 7.70 (d, 2H), 7.82 (s, 1H), 7.98 (d, 2H), 8.15-8.40 (m, 3H), 8.89 (s, 1H).

Using the same procedure but replacing the 5-nitro-benzothiophene-2-carbonyl chloride by:

6-methoxy-benzothiophene-3-acetyl chloride (described by Sauter F., Monatshefte Fuer Chemie, 1968, 99, 2, 610-15) the following compound was obtained:

N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)-2-(6-methoxy-benzothien-3-yl)acetamide

EXEMPLE 8

N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)-2-(6-methoxy-benzothien-3-yl)acetamide

mp: 104°C

^{1}H-NMR (DMSO d_6): 3.75-3.85 (m, 5H), 7.02 (dd, 1H), 7.13 (s, 1H), 7.30 (s, 1H), 7.50-7.75 (m, 4H), 7.80 (s, 1H), 7.90 (d, 2H), 8.25 (s, 1H).

EXEMPLE 9

4-{N-[1H-imidazol-1-yl]-N-[(6-methoxy-benzothien-3-yl)methyl]amino}benzonitrile

3-Chloromethyl-6-methoxy-benzothiophene (12.35 g, 58.06 mmol) was added to a mixture of 4-[N-(1H-imidazol-1-yl)amino]benzonitrile (9.72 g, 52.78 mmol), K_2CO_3 (14.60 g, 105.56 mmol) and potassium iodide (0.10g, 0.60 mmol) in dry DMF (70 ml) at room temperature. The mixture was then stirred at room temperature overnight and after poured into water and extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude product as solid (14.30 g). Flash chromatography on silica gel (toluene / dioxan: 6/4) yielded the expected product (10.50 g, 55 %, powder). Crystallization with ethanol yielded white crystals (7.30 g, mp: 164°C).

^{1}H-NMR (DMSO d_6): 3.80 (s, 3H), 5.25 (s, 2H), 6.74 (d, 2H), 6.93 (s, 1H), 7.02 (dd, 1H), 7.28 (s, 1H), 7.40 (s, 1H), 7.53 (s, 1H), 7.55 (s, 1H), 7.68 (d, 1H), 7.75 (d, 2H).

EXEMPLE 10

4-{N-[(6-hydroxy-benzothien-3-yl)methyl]-N-[1H-imidazol-1-yl-]amino}benzonitrile

A solution of 4-{N-[1H-imidazol-1-yl]-N-[(6-methoxy-benzothien-3-yl)methyl]amino} benzonitrile (0.50 g, 1.39 mmol) in 10 ml of methylene chloride is added at room temperature to a solution 1M of boron tribromide in methylene chloride(1.50 ml, 1.52 mmol). After 2h at room temperature the mixture was hydrolysed with saturated aqueous $NaHCO_3$, extracted with dichloromethane, dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by flash chromatography on silica gel (toluene / dioxan: 6/4) to give the expected product (0.30 g, 62 %, powder). Crystallization with ethanol yielded white crystalsl (0.10 g, mp: 167°C).

^{1}H-NMR (DMSO d_6): 5.24 (s, 2H), 6.72 (d, 2H), 6.87 (dd, 1H), 6.94 (s, 1H), 7.27 (d, 2H), 7.29 (s, 1H), 7.55 (s, 1H), 7.56 (d, 1H), 7.75 (d, 2H), 9.67 (s, 1H).

Using the same procedure but replacing the 4-{N-[1H-imidazol-1-yl]-N-[(6-methoxy-benzothiophen-3-yl)methyl]amino}benzonitrile by:
N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)-2-(6-methoxy-benzothien-3-yl)-acetamide, the following compound was obtained:
N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)-2-(6-hydroxy-benzothien-3-yl)acetamide

EXEMPLE 11

N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)-2-(6-hydroxy-benzothien-3-yl)acetamide

mp 179°C

^{1}H-NMR (DMSO d_6): 3.72 (s, 2H), 6.85 (dd, 1H), 7.10 (d, 2H), 7.25 (d, 1H), 7.40-7.70 (m, 3H), 7.80 (s, 1H), 7.91 (d, 2H), 8.24 (s, 1H), 9.60 (s, 1H).

EXAMPLE 12

5-Amino-[N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)]-benzothiophene-2-carboxamide

Stannous chloride dihydrate (13.10 g, 58.00 mmol) was added portionwise to a stirred solution of 5-nitro-[N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)]-benzothiophene-2-carboxamide (4.50 g, 11.6 mM) in ethanol (100 ml). The mixture was heated under reflux. When TLC showed complete reaction, the mixture was cooled and basified with saturated bicarbonate solution. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude product as a solid (3.90g). Crystallization from methanol yielded the expected product (2.60 g, 63%, mp: 214°C).

^{1}H-NMR ($DMSOd_6$): 6.70-6.98 (m, 3H), 7.07 (s, 1H), 7.40-7.25 (m, 4H), 7.26-7.96 (m, 3H).

EXEMPLE 13

4-[N-(6-benzyloxy-1,1-dioxido-benzothien-3-yl)-N-(1H-imidazol-1-yl)amino] benzonitrile

4-[N-(1H-imidazol-1-yl)amino]benzonitrile (0.50 g, 27.14 mmol) was added portionwise to a suspension of potassium tert-butoxide (0.35 g, 31.00 mmol) in THF (20 ml) at (10-15°C) with stirring. The mixture was stirred for 30 mn at room temperature, and then 3-bromo-6-benzyloxy-benzothiophene-1,1-dioxyde (1.10 g, 31.33 mM) in THF (5 ml) was added dropwise while keeping the temperature below 30°C. After one night, the mixture was poured into water (200 ml) and extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude product as an oil (2.50 g). Flash chromatography on silica gel (toluene / 1,4-dioxan: 7/3) and crystallisation in ethanol yielded light brown crystals (1.20 g, 95%, mp: 146°C).

^{1}H-NMR (DMSO d_6): 5.22 (s, 2H), 6.48 (s, 1H), 6.49 (d, 1H), 7.05-7.20 (m, 2H), 7.25-7.50 (m, 8H), 7.60 (d, 1H), 7.73 (s,1H), 7.94 (d, 2H).

Using the same procedure but replacing the 3-bromo-6-benzyloxy-benzothiophene-1,1-dioxyde by:

6-benzyloxy-2-(chloromethyl)-benzothiophene

the following compound was obtained:
4-[N-[(6-benzyloxy-benzothien-2-yl)methyl]-N-(1H-imidazol-1-yl)-amino]benzonitrile

EXEMPLE 14

4-[N-[(6-benzyloxy-benzothien-2-yl)methyl]-N-(1H-imidazol-1-yl)amino]benzonitrile

^{1}H-NMR (DMSO d_6): 5.12 (s, 2H), 5.30 (s, 2H), 6.72 (d, 2H), 7.00 (s, 1H), 7.04 (dd, 1H), 7.23 (s, 1H), 7.27-7.90 (m,11H).

EXEMPLE 15

4-[N-[(6-hydroxy-1,1-dioxido-benzothien-3-yl)]-N-(1H-imidazol-1-yl)amino] benzonitrile

A mixture of 4-[N-[(6-benzyloxy-1,1-dioxido-benzothien-3-yl)]-N-(1H-imidazol-1-yl) amino]benzonitrile (3.00 g, 6.78 mmol), 10% Pd/C (0.50 g), THF (30 ml) and solution of ammonium formate (25% in H_2O, 30 ml) was stirred at ambient temperature for 6 h and filtered. The mixture was poured into water and extracted with ethyl acetate, dried over Na_2SO_4, filtered, and concentrated under vacuum to give the crude product (2.50 g as solid). Crystallisation from ethanol afforded white crystals (0.80 g, 26 %, mp: 260°C).

^{1}H-NMR (DMSO d_6): 6.25 (s, 1H), 6.29 (d, 1H), 6.82 (dd, 1H), 7.10 (s, 1H), 7.15 (s, 1H), 7.30 (d, 2H), 7.70 (s, 1H), 7.91 (d,2H), 8.25 (s, 1H).

Using the same procedure but replacing the 4-[N-[(6-benzyloxy-1,1-dioxido-benzothien-3-yl)]-N-(1H-imidazol-1-yl)amino]benzonitrile by:
4-[N-[(6-benzyloxy-benzothien-2-yl)methyl]-N-(1H-imidazol-1-yl)amino]benzonitrile
the following compound was obtained:
4-[N-[(6-hydroxy-benzothien-2-yl)methyl]-N-(1H-imidazol-1-yl)amino]benzonitrile

EXAMPLE 16

4-[N-[(6-hydroxy-benzothien-2-yl)methyl]-N-(1H-imidazol-1-yl)amino]benzonitrile

mp 150°C

^{1}H-NMR (DMSO d_6): 5.15 (s, 2H), 6.63 (d, 2H), 6.80 (dd, 1H), 6.91 (s, 1H), 7.18 (d, 2H), 7.22 (s, 1H), 7.50 (s, 1H), 7.55 (d, 1H), 7.69 (d, 2H), 9.20 (s, 1H).

GENERAL PROCEDURE FOR OBTAINING SULFAMOYLATED OF COMPOUNDS (5), (7), (11) AND (13)

EXAMPLE 17

5-(Aminosulfonyl)amino-[N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)]-benzothiophene-2-carboxamide

Sulfamoyl chloride (1.90 g, 16.20 mmol) was added to a solution of 5-Amino-[N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)]-benzothiophene-2-carboxamide (2.90 g, 8.10 mmol) in dry DMAc (30 ml) with ice cooling. The mixture was then stirred at room temperature for 6 h. The mixture was poured into a satured bicarbonate solution, filtrated, washed with water and dried to give the crude product as a solid (2.70 g). Flash chromatography on silica gel (toluene / dioxan : 6/4) and crystallisation in ethanol yielded the expected product (2.60 g, 73 %, mp: 169°C).

^{1}H-NMR (DMSO d_6): 6.87 (d, 1H), 7.05-7.30 (m, 4H), 7.56 (s, 1H), 7.67 (d, 2H), 7.80-8.10 (m, 4H), 7.86 (s, 1H), 9.65 (s, 1H).

Using the same procedure but replacing the 5-Amino-[N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)]-benzothiophene-2-carboxamide by:

4-[N-[(6-hydroxy-1,1-dioxido-benzothien-3-yl)]-N-(1H-imidazol-1-yl)amino]benzonitrile

N-(4-cyanophenyl)-N-(1H-imidazol-1-yl)-2-[(6-hydroxy-benzothien-2-yl)] acetamide

4-{N-[(6-hydroxy-benzothien-3-yl)methyl]-N-[1H-imidazol-1-yl-] amino}benzonitrile

4-{N-[(6-hydroxy-benzothien-2-yl)methyl]-N-[1H-imidazol-1-yl-] amino}benzonitrile

the following compounds were respectively obtained:

Sulfamic acid 3-[N-(4-cyanophenyl)-N-(1H-imidazol-1yl)amino]-1,1-dioxido-benzothiophen-6-yl ester

Sulfamic acid 3-{2-[N-(4-cyanophenyl)-N-(1H-imidazol-1yl)amino]-2-oxoethyl}-benzothiophen-6-yl ester

Sulfamic acid 3-{[N-(4-cyanophenyl)-N-(1H-imidazol-1yl)amino]methyl}-benzothien-6-yl ester

Sulfamic acid 2-{[N-(4-cyanophenyl)-N-(1H-imidazol-1yl)amino]methyl}-benzothien-6-yl ester

EXAMPLE 18

Sulfamic acid 3-[N-(4-cyanophenyl)-N-(1H-imidazol-1yl)amino]-1,1-dioxido-benzothien-6-yl ester

mp 172°C

^{1}H-NMR (DMSO d_6): 6.24 (s, 1H), 6.29 (d, 1H), 6.85 (dd, 1H), 7.15 (s, 1H), 7.20 (s, 1H), 7.30 (d, 2H), 7.65 (s, 1H), 7.95 (d, 2H), 8.05 (s, 2H), 8.25 (s, 1H).

EXAMPLE 19

Sulfamic acid 3-{2-[N-(4-cyanophenyl)-N-(1H-imidazol-1yl)amino]-2-oxoethyl}-1,1-dioxido-benzothien-6-yl ester

mp 202°C

^{1}H-NMR (DMSO d_6): 3.70 (s, 2H), 6.85 (dd, 1H), 7.12 (d, 2H), 7.27 (d, 1H), 7.40-7.70 (m, 3H), 7.79 (s, 1H), 7.95 (d, 2H), 8.20 (s, 1H), 8.30 (d, 2H).

EXAMPLE 20

Sulfamic acid 3-{[N-(4-cyanophenyl)-N-(1H-imidazol-1yl) amino] methyl}-benzothien-6-yl ester

mp 189°C

^{1}H-NMR (DMSO d_6): 5.25 (s, 2H), 6.70 (d, 2H), 6.87 (dd, 1H), 6.91 (s, 1H), 7.22 (d, 2H), 7.25 (s, 1H), 7.50 (s, 1H), 7.56 (d, 1H), 7.70 (d, 2H), 8.10 (s, 2H).

EXAMPLE 21

Sulfamic acid 2-{[N-(4-cyanophenyl)-N-(1H-imidazol-1yl)amino] methyl}-benzothien-6-yl ester

mp 178 °C

^{1}H-NMR (DMSO d_6): 5.17 (s, 2H), 6.65 (d, 2H), 6.89 (dd, 1H), 6.94 (s, 1H), 7.20 (d, 2H), 7.27 (s, 1H), 7.45 (s, 1H), 7.58 (d, 1H), 7.72 (d, 2H), 8.00 (s, 2H).

The following examples are intended to illustrate and not to limit the scope of the invention.

BIOLOGICAL PROTOCOLS

INHIBITION OF STEROID SULFATASE, AROMATASE AND CARBONIC ANHYDRASE II *IN VITRO*

Estrone sulfate (E_1S) is a major circulating plasma estrogen that is converted by the steroid sulfatase enzyme into estrone (E_1), which in turn can be transformed into estradiol (E_2) by enzymatic reduction.

The reduction of E_2 synthesis by aromatase inhibitors has been clinically proved to be the best way to halt the progress of hormone-dependent breast tumors. In the following experiments, we have shown that compounds with both aromatase and steroid sulfatase activities are a suitable approach to inhibit tumor growth.

Human carbonic anhydrases catalyse the conversion between carbon dioxide (CO_2) and the bicarbonate ion (HCO_3^-), and are involved in physiological and pathological processes. They include hormone-dependent and non-hormone-dependent cancerogenesis, metastasis process and hypoxic tumors which express these enzymes that are less responsive to classical chemo/radio-therapy. In particular, EMATE was found to have a human carbonic anhydrases inhibitory potency similar to that of acetazolamide, a well-known sulfonamide human carbonic anhydrases inhibitor.

Aromatase activity, Methods & Materials

The JEG-3 cell line over-expresses human aromatase. 24 hours before measurement, cells are distributed for seeding in 96-well microplates, 24 hours

later, microplates are rinsed and fresh medium containing the radioactive aromatase substrate (1β-^{3}H-androstenedione, 10 nM) is added together with test compounds dissolved with 1 % dimethylsulfoxide in a test concentration range between 10^{-11} and 10^{-4} M in a total volume of 150 µl. Two hours after the beginning of the incubation, 100 µl of the supernatants are transferred to homologous new 96-well microplates. A solution of dextran-coated charcoal (1 %) is added in each well (100 µl/well); after standing on ice for 10 minutes, microplates are centrifuged (1500 g; 4°C). All steroids, including the radioactive substrate and the test compounds, are adsorbed on charcoal; only ^{3}H-water specifically formed during aromatisation of 1β-^{3}H-androstenedione, involving a specific oxidative step removing the 1β-^{3}H, remains in the supernatant at this stage. Supernatants receive a scintillation cocktail for β-radioactivity measurement. In parallel, the aromatase reaction is stopped in the microplates by destruction and solubilization of the cells in a 10 mM ethylenediamine tetraacetate solution at pH 12.3. Then, DNA is measured by a standard fluorimetric method using the Hoechst 33258 fluorochrome and a microplate fluorimeter (Wallac, model 1420 Victor^2). Finally, aromatase activity is expressed in fmoles/µg DNA in 2 hours and aromatase inhibition as a percentage of that observed in a control incubation without inhibitors. A non-linear fit analysis of % of inhibition *vs.* concentration allows the determination of the 50 % inhibitory concentration (IC_{50}): the lowest IC_{50} correspond to the most potent inhibitors.

Steroid sulfatase activity, Methods & Materials

The JEG-3 cell line is very rich in human estrone sulfatase. Assays are carried out with cells in logarithmic growth phase on 96-well microplates. 24h before studies, cells are seeded in decomplemented fetal calf serum (dFCS) supplemented medium. Then, the seeding medium is removed and the cells are rinsed with PBS to eliminate any trace of dFCS. Then ^{3}H-E_1S is added, followed by test compounds at concentrations ranging from 10^{-12} M to 10^{-5} M. After 4 h of treatment, the medium is transferred into 96-deep-well microplates and centrifuged at 200 x g for 10 min to pellet cells before toluene extraction. A fraction of medium is used for toluene extraction in order to separate the conjugated substrate from non-conjugated products. The radioactivity in the toluene phase is measured by liquid scintillation counting. Finally, estrone

sulfatase activity is expressed in pmoles of ^3H-E_1 + ^3H-E_2 formed per 4 hours and per µg DNA, and estrone sulfatase inhibition as a percentage of control activity without inhibitor. A non linear fit analysis (GraphPad Prism Software) of % inhibition *vs.* inhibitor concentrations allows the determination of the 50 % inhibitory concentration (IC_{50}): the lowest IC_{50} corresponds to the most potent inhibitors.

Alkaline phosphatase activity, Methods & Materials

To evaluate the estrogenic potency of test compounds, the well-established Ishikawa cell model is used. Cells are routinely grown in a medium containing 10% dFCS. Seeding is performed in Nunc culture plastic flasks and cells are maintained in a humidified atmosphere of 5% CO_2 and 95% air at 37±0.1 °C. The effect of the test compounds on alkaline phosphatase induction is measured in estrogen-free medium. Briefly, cells are seeded into 96-well microplate 48 h before studies. At the end of a 4-day treatment, alkaline phosphatase activity is measured with the *p*-nitrophenyl-phosphate assay, and the activity is expressed as n-fold increase with respect to control levels, then as a percentage of the activity recorded in the presence of 10^{-8} M E_2, which is taken to be equal to 100%.

Human carbonic anhydrase II activity, Methods & Materials

This assay is performed as described in the literature (Armstrong J. et al. Purification and properties of human erythrocyte carbonic anhydrases, J Biol Chem, 1966, 241: 5137-5149). Briefly, in this assay, human carbonic anhydrase II catalyses the conversion of *p*-nitrophenyl acetate into *p*-nitrophenol. The potential inhibitory effect of test compounds is evaluated by colorimetric determination of *p*-nitrophenol produced during the enzymatic reaction. The optical density levels obtained without inhibitor are referred to as "total activity". The levels obtained without inhibitor and without the enzyme are referred to as "blank" in order to assess any interference with the substrate during the assay.

ANTI UTEROTROPHIC/ANTI STEROID SULFATASE ACTIVITY *IN VIVO*

Wistar female rats are ovariectomized and left to rest for 4 weeks. Prior to treatment, the absence of cyclicity is checked by vaginal smears. Animals are

supplemented with estrone sulfate (E_1S) at 50 µg/kg/day s.c., alone or combined with oral administration of potential sulfatase inhibitors, at 1 mg/kg/day for 4 days. The uteri are removed, freed of adjacent tissue and wet weighed. The antagonist effect of the tested compounds against estrone sulfate uteri weight increase, corresponds to the sulfatase inhibition potency of said compounds.

Estrone sulfatase activity is measured according to the method described by Purohit et al., with slight modifications. Briefly, uteri are thawed, weighed and homogenized. Aliquots of the supernatant are treated with dextran-coated charcoal and assayed for sulfatase. E_1S activity is assessed after 30 min of incubation with 5 nM of ^3H-E_1S and 20 µM of unlabelled E_1S as substrate. Estrone sulfatase activity is expressed as pmol /h/mg protein and reported as percentage of inhibition *vs* E_1S; for uteri weights, results are expressed as % of inhibition of the E_1S induced stimulation.

INHIBITION OF ESTRADIOL PEAK, AS *IN VIVO* AROMATASE INHIBITION MODEL

The aim of this experimentation is to determine a dose-related activity of test compounds in comparison with anastrozole on 17β-estradiol level 24 hours after one oral administration in female rats. Anastrozole, is a potent, non steroidal inhibitor of aromatase, which significantly inhibits estradiol levels from 3 µg/kg, 24 hours after one single oral administration in female rats. One hundred IOPS Wistar female rats, weighing 180 to 200 g, are accommodated by four in stainless steel mesh cages. Animals are allowed free access to a standard diet from Harlan Teklad 2016 pellets. Vaginal smears are performed for each animal, each morning, in order to establish the different phases of cycle. The rats which do not exhibit a regular estrous cycle, are excluded from the experimentation. Starting at 4.00 pm, animals receive an oral administration of formulations. 24 hours later, samples of serum are collected and estradiol level are determined as previously described.

INHIBITION OF TUMOR GROWTH

MCF-7 xenograft into nude mice

MCF-7 cells, derived from human breast adenocarcinoma, are injected subcutaneously in ovariectomized athymic nude mice supplemented with a daily administration of subcutaneous estrone sulfate. Xenograft volumes are determined weekly. When tumor volumes reach a significant increase, test compounds are orally administered from 0.1 to 1mg/kg/day for 4 or 8 weeks. Xenografts are measured, removed, weighed, and deep frozen until the determination of sulfatase activity and intratumoral estradiol level, according to the above-mentioned methods.

JEG-3 xenograft into nude mice

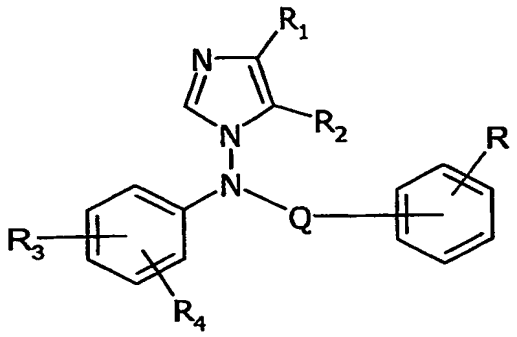
The JEG-3 cell line over-expresses both human aromatase and estrone sulfatase enzymes. It is injected subcutaneously into ovariectomized athymic nude mice supplemented with a daily administration of subcutaneous estrone sulfate with or without test compounds (administered at 5mg/kg/day). Enzyme activities and plasma levels of estrone sulfate and estradiol are determined according to the above-mentioned methods.

JEG-3 xenograft within nude rat supplemented with estrone sulphate and Δ4-androstenedione

15 days before JEG-3 cell injection into rats, blood samples are taken to measure basal plasma estradiol levels. Then, JEG-3 cells are injected subcutaneously in ovariectomized athymic (Rnu/Rnu) nude rat. Animals are supplemented with a daily administration of subcutaneous estrone sulphate and Δ4-androstenedione with or without test compounds (administered at from 0.1 to 1mg/kg/day). After a 21-day period, blood sampling are performed one day after cancerous xenograft and at the end of the experiment. In this experiment estrone sulfate and Δ4-androstenedione are the precursors of estradiol. The effect of estradiol is reflected on the uterus weight after sacrifice, and sulfatase inhibition is shown by the anti-uterotrophic potency of compounds. Plasma hormone levels are assayed at the end of the experiments according to the supplier's standard method (DSL,Webster,TX,USA).

CLAIMS

1. A compound of formula (I):



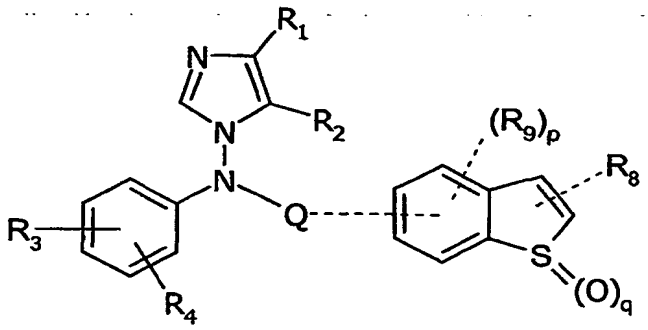
(I)

and acid addition salts and stereoisomeric forms thereof, wherein:

- R_1 and R_2 are each independently hydrogen, a $(C_1$-$C_6)$alkyl or a $(C_3$-$C_8)$cycloalkyl ; or R_1 and R_2 together form a saturated or unsaturated 5-, 6- or 7- membered carbocyclic ring;
- Q is $(CH_2)_m$-X-$(CH_2)_n$-A-;
- A is a direct bond or O, S, SO, SO_2, NR_5;
- X is a direct bond, CF_2, O, S, SO, SO_2, C(O), NR_5 or CR_6R_7;
- m and n are each independently 0, 1, 2, 3 or 4;
- R_3 and R_4 are each independently a $-(CY_1Y_2)_r$-Z group;
- Z is hydrogen or a hydroxy, cyano, halogen, nitro, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, benzyloxy, trifluoromethyl, $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylsulfonyl, acyl, $(C_1$-$C_6)$alkoxycarbonyl, $-NR_{10}R_{11}$, $-OPO(OR_{10})_2$, -OCHO, $-COOR_{10}$, $-SO_2NR_{10}R_{11}$, $-OSO_2NR_{10}R_{11}$, $-SO_2OR_{10}$, $-OSO_2OR_{10}$, $-SSO_2NR_{10}R_{11}$, $-CONR_{10}R_{11}$, $-OCONR_{10}R_{11}$, $-OCSNR_{10}R_{11}$, $-SCONR_{10}R_{11}$, $-SCSNR_{10}R_{11}$, $-NR_{12}SO_2NR_{10}R_{11}$, tetrazolyl, $-NR_{10}CONR_{11}OH$, $-NR_{10}SO_2NR_{11}OH$, -NOH-CHO, $-NOHSO_2NR_{10}R_{11}$, or $-OSO_2NR_{10}OH$ group;
- Y_1 and Y_2 are each independently H or F;
- r is 0, 1 or 2;
- R_5, R_6, R_7, R_{10}, R_{11} and R_{12} are each independently hydrogen, a $(C_1$-$C_6)$alkyl or a $(C_3$-$C_8)$cycloalkyl; R_{10} can also be a salt; R_{10} and R_{11} can also form, together with the nitrogen atom to which they are bound, a 5- to 7-membered heterocycle containing one or two heteroatoms selected from O, S and N;

- the aromatic ring together with the R group represent a moiety that inhibits the sulfatase enzyme.

2. A compound according to claim 1, of formula (II):



(II)

wherein:

- R_1, R_2, R_3, R_4 and Q are as defined for the compounds (I) in claim 1;
- R_8 and R_9 are each independently a $-(CY_1Y_2)_r-Z$ group;
- Y_1, Y_2 and Z are as defined for the compounds (I) in claim 1;
- p is 1, 2, 3 or 4; when p is 2, 3 or 4 the radicals R_9 can be the same or different;
- q is 0,1 or 2.
- The dotted line means that Q and/or R_8 and/or R_9 can be on any position of the benzothiophene ring.

3. A compound according to claim 2, wherein R_8 is $-OSO_2NR_{10}R_{11}$, $-NR_{12}SO_2NR_{10}R_{11}$

4. A compound according to claim 2 or 3, wherein R_9 is hydrogen, halogen, nitro, $COOR_{10}$, cyano.

5. A compound according to one of claims 1 to 4, wherein R_4 is hydrogen, halogen, cyano, (C_1-C_6)alkoxy, $-NR_{10}R_{11}$, $-OSO_2NR_{10}R_{11}$ or $-NR_{12}SO_2NR_{10}R_{11}$

6. A compound according to one of claims 1 to 5, wherein R_{10}, R_{11} and R_{12} are each independently hydrogen or $(C_1$-$C_6)$alkyl.

7. A compound according to one of claims 1 to 6, wherein Q is $-(CH_2)_m$-X- where m is 0, 1 or 2 and X is a direct bond, SO_2 or CO.

8. A compound according to one of claims 1 to 7, wherein R_1 and R_2 are each independently hydrogen or $(C_1$-$C_6)$alkyl.

9. A compound according to one of claims 1 to 8, wherein R_3 is hydrogen, halogen, cyano.

10. A compound according to one of claims 1 to 9 or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

11. A pharmaceutical composition comprising a compound according to one of claims 1 to 9, or a pharmaceutically acceptable acid addition salt thereof, and a pharmaceutical acceptable carrier.

12. A pharmaceutical composition according to claim 11, comprising from 0.1 to 400 mg of said compound.

13. Use of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment or prevention of hormone- or non hormone-dependent tumors, wherein said compound is optionally combined with a sexual endocrine therapeutic agent.

14. Use of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the control or management of reproductive functions, wherein said compound is optionally combined with a LH-RH agonist or antagonist, an

estroprogestative contraceptive, a progestin, an anti-progestin or a prostaglandin.

15. Use of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment or prevention of benign or malignant diseases of the breast, the uterus or the ovary, wherein said compound is optionally combined with an antiandrogen, an anti-estrogen, a progestin or a LH-RH agonist or antagonist.

16. Use of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment or prevention of androgen-dependent diseases or benign or malignant diseases of the prostate or the testis, wherein said compound is optionally combined with an antiandrogen, a progestin, a lyase inhibitor or a LH-RH agonist or antagonist.

17. Use of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment or prevention of cognitive function disorders.

18. Use of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment or prevention of immunodisorders.

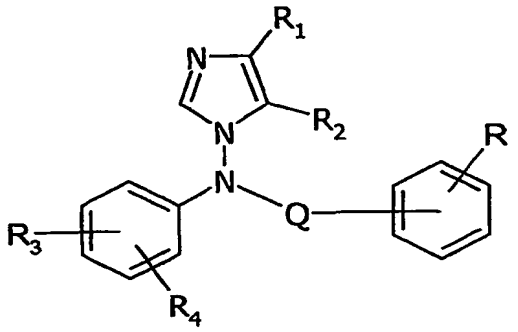
19. Use of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment or prevention of pathologies in which inhibition of aromatase and/or steroid sulfatase and/or carbonic anhydrase is required.

20. A method of treating a disease in which aromatase and/or steroid sulfatase and/or carbonic anhydrase is involved, which comprises administering

to a subject in need thereof a therapeutically effective amount of a compound according to one of claims 1 to 9.

ABSTRACT

The invention relates to the compounds of formula (I):



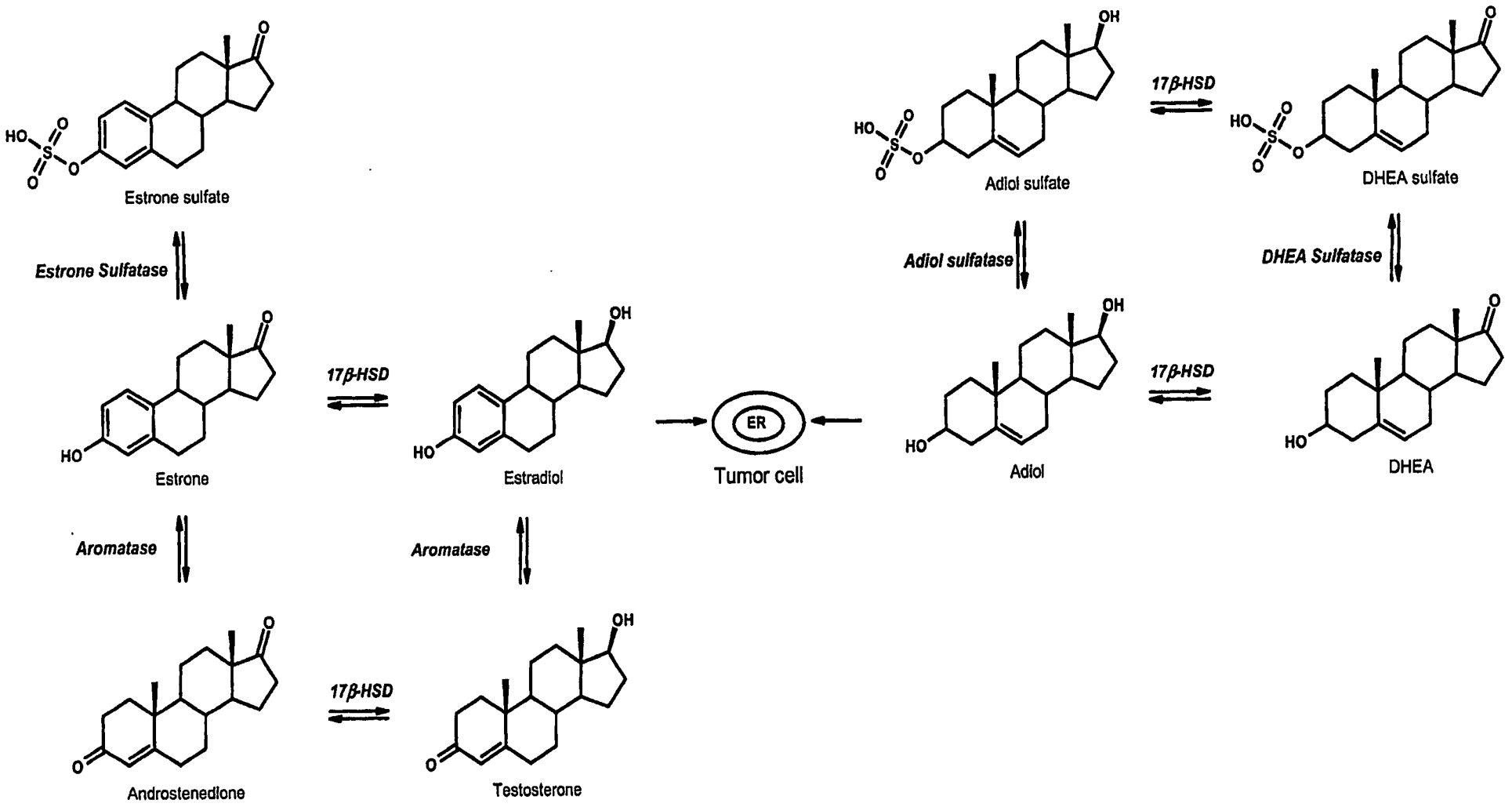
(I)

in which R_1, R_2, R_3, R_4, Q and R are as defined in the specification.

The invention also relates to the pharmaceutical compositions containing these compounds.

FIGURE 1

Formation of estrogens in Women



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